## REMARKS

### 35 USC § 112

**Claims 21-26** were rejected under 35 USC § 112 as being indefinite for use of the term "providing". The applicant disagrees for various reasons.

The term "providing" has a clear and unambiguous meaning. For example, the "Merriam-Webster Online Dictionary" (Copyright 2002 by Merriam-Webster, Incorporated) defines the above term to mean "**to supply or make available**", which will be readily understood by a person of ordinary skill in the art. Still further, the USPTO has historically recognized the term "providing" in a method claim (relating to nucleoside chemistry) as being clear and concise. This recognition is reflected, for example, in issued U.S. Pat. Nos. 5,907,036 and 5,723,589.

### 35 USC § 103

**Claims 21-26** were rejected under 35 USC § 103 as being obvious over Lam et al. (U.S. Pat. No. 5,858,670) or Carver (WO 99/64378) in view of Gravert et al. (Chemical Reviews). The applicant respectfully disagrees, especially in view of the amendments set forth herein.

Amended claim 21, and claims 22-26 by virtue of their dependence on amended claim 21 expressly require that the nucleoside library comprises a "...plurality of **modified mononucleosides**..., further specifically recites that each of the first and second nucleosides are "...**coupled to a solid support**...", and still further expressly require formation of "...a **first modified mononucleoside and a second modified mononucleoside**..."

In contrast, **Lam et al.** specifically teach random oligonucleotide libraries in which each of the oligonucleotides may be synthesized on a solid support. Clearly, the synthesis of an **oligonucleoside library teaches against the subject matter as presently claimed**. First, an oligonucleoside is simply inconsistent with a modified mononucleoside. Second, Lam et al. generate diversity by random-polymerization of selected mononucleoside, which is entirely inconsistent with generation of diversity by reacting on a solid phase mononucleosides to form modified mononucleosides.

With respect to **Carver**, the Examiner states on page 4 of the present office action that Carver teaches "..a method of synthesizing a library of nucleosides *by coupling a monomer unit to a solid support*, altering the monomer unit, then coupling another monomer units...(emphasis added)". This is not the case.

On page 11, lines 13 *et seq.* Carver teaches that "...A monomer unit is...covalently linked...to an adjoining unit...to prepare a combinatorial library of the invention...", and merely mentions that "...solid phase and solution phase chemistries may be used to synthesize a combinatorial library of the invention...". However, there is no teaching in the Carver reference that would guide a person of ordinary skill in the art as to how such solid phase chemistry would work (let alone how such chemistry would be practiced where the reagent is an amine). Thus, **Carver's suggestion of use of a solid phase chemistry completely lacks enablement** from various perspectives. Among other concerns, there is no teaching in the Carver reference which portion of the nucleoside would be coupled to the solid phase. Furthermore, in view of the nucleophilic character of the second reagent (elected species amine), and absent further description of what protecting groups, conditions, and type of solid phase coupling is employed, Carver's suggestion lacks any expectation of success. In fact, the only solid phase chemistry that had been well established at the time of filing of the present application is oligomerization and/or polymerization of protected nucleosides to form the corresponding oligomer and/or polymer.

The applicant particularly points out that modifying mononucleosides on a solid support to form a mononucleoside library (absent the applicant's inventive subject matter) is notoriously discouraging due to the presence of multiple labile chemical bonds (*e.g.*, glycosidic bond, bond to solid support) and reactive groups (*e.g.*, hydroxyl groups, amine groups, double bonds, etc.), and has not been accomplished as claimed before the applicant's filing. This is clearly reflected by a lack of references that would provide at least a reasonable expectation of success to form such libraries, and most of all, by the lack of commercially available mononucleoside libraries and compounds thereof.

This lack of reasonable expectation of success to form such libraries cannot be remedied by **Gravert** as suggested by the Examiner. On the contrary, Gravert teaches (as correctly identified by the Examiner) synthesis of an oligonucleotide on a soluble polymer wherein

hexamethylphosphoramide is employed as a coupling agent between a first and a second nucleside. Thus, and in line with previously established chemistry methods for reacting a polymer-bound nucleoside, **Gravert teaches synthesis of a oligo-/polynucleotide, which clearly teaches against the subject matter as presently claimed.**

None of the cited references, alone or in combination, provides a teaching, suggestion, and a reasonable expectation of success to form the presently claimed mononucleoside library. However, obviousness can only be established if such teaching, suggestion, and a reasonable expectation of success are present in the references (alone or combined, or combined with the knowledge of a person of ordinary skill in the art). Therefore, claims 21-26 are not obvious over Lam et al. or Carver in view of Gravert et al.

## ATTACHED MARKED-UP VERSION OF CHANGES

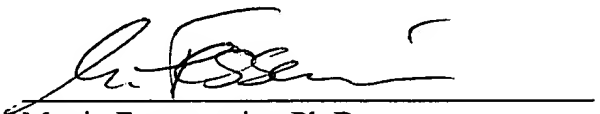
Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

## REQUEST FOR ALLOWANCE

Claims 21-26 are pending in this application. The applicant requests allowance of all pending claims.

Respectfully submitted,

Rutan & Tucker, LLP

Dated: April 14, 2003 By: 

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the Claims**

21. (Amended) A method of generating a nucleoside library comprising a plurality of modified mononucleosides, comprising:

providing a first nucleoside and a second nucleoside, each having a reactive group and each being coupled to a solid support; and

reacting the reactive group of the first and second nucleoside with a first reagent and second reagent, respectively, thereby forming a first modified mononucleoside and a second modified mononucleoside, wherein the second modified mononucleoside is chemically distinct from the first modified mononucleoside.

## CLEAN VERSION OF PENDING CLAIMS

21. A method of generating a nucleoside library comprising a plurality of modified mononucleosides, comprising:

providing a first nucleoside and a second nucleoside, each having a reactive group and each being coupled to a solid support; and

reacting the reactive group of the first and second nucleoside with a first reagent and second reagent, respectively, thereby forming a first modified mononucleoside and a second modified mononucleoside, wherein the second modified mononucleoside is chemically distinct from the first modified mononucleoside.

22. The method of claim 21 wherein at least one of the first and second nucleosides comprises a purine heterocyclic base.

23. The method of claim 21 wherein each of the first and second nucleosides comprises a sugar moiety and a heterocyclic base, and wherein the reactive group is disposed on the heterocyclic base of the first and second nucleosides.

24. The method of claim 21 wherein each of the first and second nucleosides further comprises a second reactive group.

25. The method of claim 24 further comprising a step of reacting the second reactive group of the first and second nucleoside with a third reagent and a fourth reagent, respectively.

26. The method of claim 21 wherein the first and the second reagents are selected from the group consisting of an alkyl, an aryl, an alkynyl, an alcohol, and an amine.